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Blood/gas partition coefficients of halothane, isoflurane and sevoflurane in horse blood

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Background. Blood/gas partition coefficients ($\lambda_{b/g}$) for volatile agents in horse blood are reported for halothane but not for isoflurane and sevoflurane. We measured the $\lambda_{b/g}$ of halothane, isoflurane and sevoflurane in the blood of fasted horses. The correlation with age, weight and some haematological and biochemical variables was studied. The temperature correction factor for isoflurane solubility was calculated.

Methods. Twenty-four horses were randomly allocated to halothane (n=8), isoflurane (n=8) or sevoflurane (n=8). Blood samples were taken after 10 h' fasting. Calculation of $\lambda_{b/g}$ was based on the measurement of anaesthetic partial pressures in blood at 37 °C, which was achieved with tonometer equilibration and headspace gas chromatography.

Results. Mean $\lambda_{b/g}$ was 1.66 (SD 0.06) for halothane, 0.92 (0.04) for isoflurane, and 0.47 (0.03) for sevoflurane. The $\lambda_{b/g}$ values were all significantly lower than in humans (P<0.001). No correlation was found between $\lambda_{b/g}$ and weight, age, haematocrit, plasma triglycerides, cholesterol or total bilirubin. The change in isoflurane solubility per 1 °C temperature increase was –2.63 (0.13)%.

Conclusion. The $\lambda_{b/g}$ values of halothane, isoflurane and sevoflurane in fasted horses are significantly lower than those reported in humans. The $\lambda_{b/g}$ for halothane in this study agrees with values reported in the literature but a positive correlation with plasma triglycerides could not be confirmed. Knowledge of $\lambda_{b/g}$ can refine models of anaesthetic uptake.

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The blood/gas partition coefficients ($\lambda_{b/g}$) for volatile anaesthetic agents in man are well documented.[1 2] In animals, $\lambda_{b/g}$ values for halothane are reported,[3 4] but data for isoflurane and sevoflurane are lacking. The $\lambda_{b/g}$ for halothane in the blood of horses is positively correlated with plasma triglycerides.[4] In humans, $\lambda_{b/g}$ may vary depending on the plasma composition.[5 6]

The aim of this study was to measure the $\lambda_{b/g}$ values of halothane, isoflurane and sevoflurane in the blood of fasted horses. The correlation between $\lambda_{b/g}$ and weight, age, haematocrit, plasma triglycerides, cholesterol and total bilirubin was studied. In addition, the temperature correction factor for isoflurane solubility in the horse was calculated.

Methods and results

Twenty-four healthy horses (four colts, six mares, 14 geldings) scheduled to undergo general anaesthesia for elective procedures were included in the study. They weighed 360–846 kg (mean 560 (SD 86) kg) and were 2–13 yr old (mean 8 yr).

Horses were randomly allocated by lottery to the halothane (n=8), isoflurane (n=8) or sevoflurane (n=8)

groups for measurement of $\lambda_{b/g}$. Horses were fasted for 10 h by means of muzzles but had access to water. Venous blood samples were taken by puncture of the jugular vein into one 2.5-ml EDTA vial and three heparinized 10-ml vials (Monovette®, Sarstedt, Germany).

Calculation of $\lambda_{b/g}$ was based on measurements of anaesthetic partial pressures in blood at 37 °C, which was achieved with tonometer equilibration and the headspace gas chromatography[7] analysis technique described by Zbinden and collaborators.[8] After equilibration in an IL 237 tonometer (Instrumentation Laboratory), 0.4–0.8 ml blood was transferred with a 1-ml tuberculin syringe to a 5-ml glass vial sealed with a Teflon–Neoprene septum (Supelco, USA). After equilibration for 30 min in a shaking water bath at 37 °C, a 30-µl headspace sample was transferred from the vial using a gas-tight syringe (Hamilton, Switzerland) to the gas chromatograph and analysed.

Tonometer gas-phase concentrations at 1 MAC of halothane, isoflurane and sevoflurane in air were obtained with a Vapor 19.3 vaporiser (Dräger) for halothane and isoflurane, and a Penlon vaporiser (Abbott, USA) for sevoflurane. The concentration of the resulting gas flow of 500 ml min^{-1} in the tonometer was checked with the gas chromatograph and in parallel with a calibrated Hewlett Packard M1025B (Agilent Technologies, USA) photoacoustic anaesthetic gas monitor.

For the gas chromatographic analyses, a HP 5890 Series II gas chromatograph (Agilent Technologies, USA) with flame ionization detector was used. Integration of the detector signal was managed by a HP 3396 Series II integrator (Agilent Technologies, USA). The gas flows were helium (carrier gas) 1.5 ml min^{-1}, hydrogen 30 ml min^{-1} and air 400 ml min^{-1}.

The standard curve, which relates counts to partial pressure, was obtained by injecting 30-µl samples of four different calibration gases into the gas chromatograph using a gas-tight syringe. These calibration gases were obtained by injecting 2, 10, 30 and 60 µl liquid halothane or isoflurane, and 2, 20, 40 and 80 µl liquid sevoflurane into four glass bottles (585-ml volume with a turnable stopcock and Teflon septum) after flushing the bottle with air for 5 min.

The calculated volume percent (vol%) of the volatile anaesthetics was plotted against the measured gas chromatograph counts. The partial pressure of the agent (P_{aa}) was calculated as $P_{aa} = \text{vol\%} \times P_B/100$, where P_B is the ambient barometric pressure in kPa. The range of P_{aa} of the anaesthetic calibration gases corresponded with the range of P_{aa} in the headspace of the blood samples and the gas-phase P_{aa} in the tonometer. All standard curves were linear, with a correlation coefficient of at least 0.9993. For the standard curves, the calibration mixture at each concentration point was injected five times and the mean counts calculated. The coefficient of variation was less than 1.5%. The $\lambda_{b/g}$ were calculated according to the formula given by Zbinden and colleagues.[8]

A separate study to determine the temperature correction factor for isoflurane in the horse was performed. Blood from three horses was tonometered with isoflurane 1.3%. Equilibration for at least 15 min was allowed at temperatures of 33, 35, 37 and 39 °C. Eight 0.5-ml blood samples were withdrawn from the tonometer at each temperature. Each sample was placed in a 5-ml vial and equilibrated with the headspace in a shaking water bath at the corresponding temperature. Headspace samples were measured in triplicate by gas chromatography. The coefficient of variation was 2.7%.

Plasma triglycerides were measured using an enzymatic/colorimetric method (Triglycerides GPO–PAP, Roche Diagnostic GmbH, Germany).

A univariate linear regression analysis was performed (SPSS version 10, USA) to study the relationship between the $\lambda_{b/g}$ of each anaesthetic agent and the independent variables of weight, age, haematocrit, plasma triglycerides, cholesterol and total bilirubin. The level of significance was set at $P<0.05$.

Values for $\lambda_{b/g}$ are expressed as mean (SD) of 7–10 blood measurements for each horse. Mean $\lambda_{b/g}$ was 1.66 (0.07) for halothane, 0.92 (0.04) for isoflurane, and 0.47 (0.03) for sevoflurane. They were significantly different for each anaesthetic agent (one-way ANOVA; $P<0.001$). Plasma concentrations of triglycerides and total bilirubin were higher than normal in three of the 24 horses, and cholesterol concentrations were lower than normal in ten horses (Table 1). No significant dependence of $\lambda_{b/g}$ on age, weight, haematocrit, plasma triglycerides, cholesterol or total bilirubin was found.

The temperature correction for isoflurane partial pressure was shown to follow an exponential course: $P_{iso} = P_{37iso} \times 10^{-0.02199\times(T-37)}$, where P_{iso} is the partial pressure corrected for temperature, P_{37iso} is the measured isoflurane partial pressure at 37 °C, and T is the temperature (°C). The change in isoflurane solubility per 1 °C temperature increase was –2.63 (0.13)%.

Comment

In horses, sevoflurane is the least soluble of the three volatile agents, isoflurane being intermediate, which is consistent with the $\lambda_{b/g}$ values in man of 0.62 (0.04) for sevoflurane, 1.27 (0.06) for isoflurane and 2.46 (0.09) for halothane reported by Yasuda and colleagues.[1] The $\lambda_{b/g}$ values in horses were 32.5% (halothane), 27.5% (isoflurane) and 24.2% (sevoflurane) lower than in man.[1] This difference is highly significant ($P<0.001$) for each agent but the reason is unclear. Whether a change in $\lambda_{b/g}$ in horse blood occurs with changing pH is also unknown.

Weaver and Webb[4] found a weak but significant correlation between the $\lambda_{b/g}$ of halothane and plasma triglycerides.[6] A possible influence of fasting on $\lambda_{b/g}$ was suggested, as horses typically mobilize fat when fasted and develop hyperlipidaemia. In the current study, the concentrations of

Table 1 Haematological, biochemical and blood/gas partition coefficient ($\lambda_{b/g}$) values. Normal values: haematocrit 0.34–0.45 litre^{-1}, cholesterol 2.05–3.04 mmol litre^{-1}, total bilirubin 8.55–47.9 μmol litre^{-1}, triglycerides 0.08–0.38 mmol litre^{-1}. Values for $\lambda_{b/g}$ are mean (SD) of 7–10 blood measurements for each horse. Groups: H, halothane; I, isoflurane; S, sevoflurane

Horse	Group	Haematocrit (litre^{-1})	Cholesterol (mmol litre^{-1})	Total bilirubin (μmol litre^{-1})	Triglycerides (mmol litre^{-1})	$\lambda_{B/G}$
1	H	0.30	1.89	21.3	0.15	1.66 (0.07)
2	H	0.33	1.85	29.4	0.39	1.74 (0.07)
3	H	0.40	2.8	31.4	0.41	1.64 (0.07)
4	H	0.29	1.96	20.9	0.35	1.70 (0.08)
5	H	0.32	2.40	71.6	0.32	1.62 (0.05)
6	H	0.30	1.70	36.4	0.26	1.65 (0.07)
7	H	0.43	2.55	33.6	0.28	1.66 (0.07)
8	H	0.48	2.41	44.4	0.18	1.63 (0.06)
9	I	0.36	3.03	35.5	0.34	0.91 (0.03)
10	I	0.42	2.94	39.2	0.24	0.87 (0.04)
11	I	0.33	2.01	32.3	0.17	0.95 (0.03)
12	I	0.34	2.23	36.6	0.34	0.94 (0.04)
13	I	0.37	2.38	40.5	0.29	0.96 (0.03)
14	I	0.29	2.02	21.9	0.29	0.89 (0.04)
15	I	0.33	2.03	27.1	0.21	0.90 (0.04)
16	I	0.35	1.55	30.0	0.22	0.91 (0.04)
17	S	0.41	2.62	35.6	0.28	0.46 (0.02)
18	S	0.36	1.85	18.3	0.23	0.48 (0.01)
19	S	0.37	2.61	60.9	0.27	0.46 (0.07)
20	S	0.30	2.17	34.2	0.40	0.47 (0.08)
21	S	0.37	2.98	55.1	0.22	0.47 (0.007)
22	S	0.30	1.94	17.2	0.14	0.46 (0.01)
23	S	0.35	2.92	30.2	0.27	0.47 (0.01)
24	S	0.39	2.38	29.0	0.33	0.46 (0.01)

plasma triglycerides and total bilirubin were measured after the usual 10-h of fasting, but consistent hypertriglyceridaemia and hyperbilirubinaemia are not seen until after 48 h of fasting in horses.[9] It is therefore not surprising that a dependence of $\lambda_{b/g}$ on plasma triglycerides could not be confirmed in this study. Routine preoperative fasting does not seem to affect $\lambda_{b/g}$ in horses.

Blood solubility of isoflurane increases with decreasing temperature. The percentage change in isoflurane solubility per 1 °C increase in temperature measured in horses (–2.63) was lower than the values reported by Eger and colleagues[10] in man (–4.36).

Knowledge of the specific $\lambda_{b/g}$ for the horse can be used to refine models of anaesthetic uptake in this species. When exact measurements of anaesthetic partial pressures are required, the influence of temperature has to be taken into account.

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References

1 Yasuda N, Eger EI, Weiskopf RB, Tanifuji Y, Kobayashi K. Solubility of desflurane (I-653), sevoflurane, isoflurane and halothane in human blood. *Masui* 1991; **40**: 1059–62

2 Steward A, Allott P, Cowles AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil and biological media. *Br J Anaesth* 1973; **45**: 282–93

3 Steward A, Allott P, Mapleson WW. The solubility of halothane in canine blood and tissues. *Br J Anaesth* 1975; **47**: 423–34

4 Weaver BMQ, Webb AI. Tissue composition and halothane solubility in the horse. *Br J Anaesth* 1981; **53**: 487–93

5 Malviya S, Lerman J. The blood/gas solubilities of sevoflurane, isoflurane, halothane and serum constituent concentrations in neonates and adults. *Anesthesiology* 1990; **72**: 793–6

6 Saraiva RA, Willis BA, Steward A, Lunn JN, Mapleson WW. Halothane solubility in human blood. *Br J Anaesth* 1977; **49**: 115–9

7 Ettre LS. Headspace–Gas chromatography: an ideal technique for sampling volatiles present in non-volatile matrices. *Adv Exp Med Biol* 2001; **488**: 9–32

8 Zbinden AM, Frei FJ, Funk B, Thomson DA. Determination of the partial pressure of halothane (or isoflurane) in blood. *Br J Anaesth* 1985; **57**: 796–802

9 Bauer JE. Plasma lipids and lipoproteins of fasted ponies. *Am J Vet Res* 1983; **44**: 79–84

10 Eger RR, Eger EI II. Effect of temperature and age on the solubility of enflurane, halothane, isoflurane and methoxyflurane in human blood. *Anesth Analg* 1985; **64**: 640–2